IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
WOLFMAN *et al.*	)	Group Art Unit: 1649
	)	
Application No.: 10/689,677	)	Examiner: Aditi Dutt
	)	
Filed: October 22, 2003	)	Confirmation No.: 2405
	)	
For: ACTRIIB Fusion Polypeptides and Uses Therefor	)	
	)	
	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION OF DR. PAUL YAWORSKY UNDER 37 C.F.R. § 1.132

I, Paul Yaworsky, declare:

1. I am an Associate Director, Women's Health and Musculoskeletal Biology, at Wyeth and have been employed at Wyeth (and its predecessor company, Genetics Institute) in various scientific capacities since March, 1998. I received my Ph.D. in Molecular Neuroscience from the Mayo Clinic in 1997, and my B.A. in Molecular Genetics from the University of Toronto in 1989.

2. I have reviewed and understand U. S. Patent Application No.10/689,677 (the '677 application), in the name of inventor Neil M. Wolfman, including the pending

claims. The claims of the '677 application relate to methods for administering ActRIIB-Fc fusion polypeptides for the treatment of muscular and neuromuscular diseases and/or disorders.

3. As part of my work at Wyeth, my research group has confirmed the utility of the methods described and claimed in the '677 application, involving the ability of ActRIIB-Fc fusion polypeptides to increase muscle mass and strength *in vivo*. The following data demonstrate that administration of an ActRIIB-Fc fusion polypeptide increases muscle mass and strength in an *in vivo* animal model of muscular dystrophy, *mdx* mouse model[1]. The experiments described here were conducted between July 30, 2007 and October 22, 2007.

4. We prepared a human ActRIIB fusion protein comprising amino acids 23-138 of SEQ ID NO: 3 fused to the Fc region of a human IgG1 immunoglobulin (ActRIIB-Fc fusion polypeptide). Four week old *mdx* male mice were dosed weekly by IP injection with a total weekly dose of 10 mg/kg, per animal for twelve weeks. As a control, another cohort of mice were given a weekly injection of PBS.

[1] "*mdx*" mice were purchased from Jackson Laboratories, and have the genotype designation C57BL/10ScSn-Dmd^{mdx}/J. *Mdx* mice have a mutation in the dystrophin gene, and therefore are commonly used to study Duchenne muscular dystrophy. See, for example, Bogdanovich et al. (2002), *Nature* 420:418-421.

ActRIIB-Fc Increases Muscle Strength in *mdx* Mice

5. As shown in Figure 1, *mdx* mice that received 10 mg/kg of the ActRIIB-Fc fusion protein had significantly improved muscle strength, as evidenced by increased grip strength, compared to PBS controls. As noted above, these results demonstrate that administration of ActRIIB-Fc increases muscle strength in *mdx* mice.

Figure 1

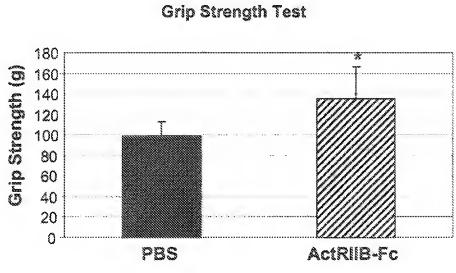

Figure 1 shows grip strength, in grams. The asterisk symbol (*) indicates a statistically significant difference ($p<.01$).

ActRIIB-Fc Increases Muscle Mass in *mdx* Mice

6. As shown in Figure 2, when *mdx* mice were given 10 mg/kg of the ActRIIB-Fc fusion protein, muscle mass of both the gastrocnemius and quadriceps muscles were significantly increased, as compared to PBS controls. Our results further demonstrate that administration of ActRIIB-Fc also increases muscle mass in *mdx* mice.

Figure 2

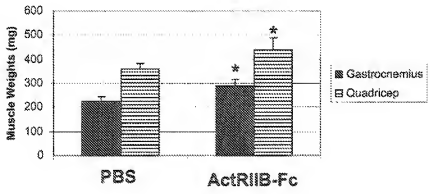

Figure 2 shows muscle weights of the gastrocnemius and quadriceps muscles, in milligrams. The asterisk symbol (*) indicates a statistically significant difference ($p<0.001$), when compared with PBS treated control mice. Gastrocnemius muscle is shown by the dark bars, and quadriceps muscle is shown by the striped bars.

7. In summary, administration of the ActRIIB-Fc fusion protein to *mdx* mice increased muscle strength and muscle mass (of both the gastrocnemius and the quadriceps muscle). These studies demonstrate that ActRIIB-Fc fusion polypeptide functions *in vivo* to increase muscle strength and mass in an *in vivo* animal model of muscular dystrophy.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: March 3 '08

By: _____

Paul Yaworsky, Ph.D.
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